IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE

PAR PHARMACEUTICAL, INC., PAR STERILE PRODUCTS, LLC, and ENDO PAR INNOVATION COMPANY, LLC,	)	
Plaintiffs,	)	C.A. No. 18-823-CFC-JLH
v.	)	
EAGLE PHARMACEUTICALS INC.,	)	
Defendant.	)	

PAR'S PROPOSED FINDINGS OF FACT REGARDING EAGLE'S INFRINGEMENT OF THE '209 AND '785 PATENTS

Dated: July 19, 2021

OF COUNSEL:

Martin J. Black
Sharon K. Gagliardi
Brian M. Goldberg
Luke M. Reilly
Daniel R. Roberts
DECHERT LLP
Cira Centre
2929 Arch Street
Philadelphia, PA 19104
Tel: (215) 994-4000
martin.black@dechert.com
sharon.gagliardi@dechert.com
brian.goldberg@dechert.com
luke.reilly@dechert.com
daniel.roberts@dechert.com

Brian E. Farnan (Bar No. 4089)
Michael J. Farnan (Bar No. 5165)
FARNAN LLP
919 North Market St.
12th Floor
Wilmington, DE 19801
Tel: 302-777-0300
Fax: 320-777-0301
bfarnan@farnanlaw.com
mfarnan@farnanlaw.com

Attorneys for Plaintiffs Par Pharmaceuti
Inc., Par Sterile Products, LLC, and End
Par Innovation Company, LLC

Robert D. Rhoad
DECHERT LLP
502 Carnegie Center, Suite 104
Princeton, NJ 08540-7814
Tel: (609) 955-3200
robert.rhoad@dechert.com

Jonathan D. J. Loeb, Ph.D
DECHERT LLP
2400 W. El Camino Real, Suite 700
Mountain View, CA 94040-1499
Tel: (650) 813-4995
jonathan.loeb@dechert.com

Blake B. Greene
DECHERT LLP
300 W. 6th Street, Suite 2010
Austin, TX 78701
Tel: (512) 394-3000
blake.greene@dechert.com

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I. THE PARTIES

1. Plaintiff Par Pharmaceutical, Inc. ("Par Pharmaceutical") is a corporation organized and existing under the laws of the State of New York, having a principal place of business at 1 Ram Ridge Road, Chestnut Ridge, New York 10977. Par Pharmaceutical develops, manufactures, and markets pharmaceutical products in the United States. D.I. 268, *Par v. Eagle* Pretrial Order (*hereinafter* "PTO"), Ex. 1 ¶ 1.

2. Plaintiff Par Sterile Products, LLC ("Par Sterile Products") is a limited liability company organized and existing under the laws of Delaware, having its principal place of business at 1 Ram Ridge Road, Chestnut Ridge, New York 10977. Par Sterile Products develops, manufactures, and markets injectable pharmaceutical products, and provides manufacturing services to the biopharmaceutical and pharmaceutical industry. PTO Ex. 1 ¶ 2.

3. Plaintiff Endo Par Innovation Company ("EPIC") is a limited liability company organized and existing under the laws of Delaware, having its principal place of business at 1 Ram Ridge Road, Chestnut Ridge, New York 10977. PTO Ex. 1 ¶ 3.

4. Plaintiffs Par Pharmaceutical, Par Sterile Products, and EPIC are referred to collectively as "Par." PTO Ex. 1 ¶ 4.

5. Defendant Eagle ("Eagle") is a corporation organized under the laws of the State of Delaware having a principal place of business at 50 Tice Road, Suite 315, Woodcliff, New Jersey, 07677. Eagle develops and markets pharmaceutical products, including injectable pharmaceutical products, in the United States. PTO Ex. 1 ¶ 5.

6. Non-party Albany Molecular Research Inc. ("AMRI") and its subsidiary OSO were also referred to at trial. AMRI is Eagle's drug product manufacturer who made Eagle's vasopressin batches. *See* PTX-1435, at 4, 20, 25; PTX-1443 (Aungst 2021 Tr.) 20:19-22. AMRI will also be the manufacturer of Eagle's ANDA product if the United States Food and Drug Administration ("FDA") approves Eagle's ANDA. DTDX-1 (Aungst 2019 Tr.) 46:3-46:6. After manufacture, AMRI will transfer the product to Eagle, which will subsequently market and sell Eagle's ANDA product. DTDX-1 (Aungst 2019 Tr.) 46:7-13.

II. THE HATCH-WAXMAN ACT FRAMEWORK

7. A company seeking to market a new pharmaceutical drug in the United States must first obtain approval from the FDA, typically through the filing of a New Drug Application ("NDA"). *See* 21 U.S.C. § 355(a), (b). The sponsor of the NDA is required to submit to FDA information on all patents claiming the drug that is the subject of the NDA, including any amendments or supplements thereto, or a method of using that drug, and FDA then lists the patent information in its

publication, the *Approved Drug Products with Therapeutic Equivalence Evaluations*, which is referred to as the "Orange Book." *See* 21 U.S.C. § 355(b)(1) and (c)(2); 21 C.F.R. 314.53(b)(1).

8. Alternatively, a company seeking to market a generic version of a previously approved drug is not required to submit a full NDA. Instead, it may file an Abbreviated New Drug Application ("ANDA"). *See* 21 U.S.C. §355(j). The generic drug approval process is considered "abbreviated" because the generic manufacturer may piggyback on the innovator company's data and FDA's prior finding of safety and efficacy by demonstrating, among other things, that the generic product is bioequivalent to the previously approved drug (the "listed drug" or "branded drug"). *See* 21 U.S.C. §355(j)(2)(A)(iv); *Eli Lilly & Co v. Medtronic, Inc.*, 496 U.S. 661, 676 (1990).

9. In conjunction with this "abbreviated" application process, Congress has put in place a process for resolving patent disputes relating to generic drugs, pursuant to which an ANDA filer must provide certifications addressing each of the patents listed in the Orange Book for the branded drug. *See* 21 U.S.C. § 355(j)(2)(A)(vii); 21 C.F.R. § 314.94(a)(12). An ANDA filer may certify, for instance, that it believes a patent is invalid or will not be infringed by the manufacture, use, or sale of the generic drug for which the ANDA is submitted

(this is referred to as a "Paragraph IV Certification"). *See* 21 U.S.C. § 355(j)(2)(A)(vii)(IV); 21 C.F.R. § 314.94(a)(12)(i)(A)(4).

10. The filer of an ANDA with a Paragraph IV Certification must also provide notice to both the owners of the listed patents and the holder of the NDA for the referenced listed drug. This "Paragraph IV Notice" must include a detailed statement of the factual and legal bases for the applicant's belief that the challenged patent is invalid or not infringed by the proposed generic product. 21 U.S.C. § 355(j)(2)(B); 21 C.F.R. § 314.95.

11. If the patentee or NDA holder files a patent infringement action within 45 days of receiving a Paragraph IV Notice from an ANDA filer, final approval of the ANDA is subject to a 30-month stay. *See* 21 U.S.C. § 355(j)(5)(B)(iii); 21 C.F.R. § 314.107(b)(3). The 30-month stay is important to the innovator companies because it protects them from the harm that could otherwise ensue from the FDA granting approval to an infringing product without first providing an opportunity for the infringement case to be resolved, such that the innovator company is assured of a 30-month period during which it may try to enforce its intellectual property rights and resolve any patent dispute before the generic product enters the market. *See* 21 U.S.C. § 355(j)(5)(B)(iii).

III. VASOPRESSIN BACKGROUND

12. Vasopressin is a peptide drug that causes contraction of vascular and other smooth muscle cells. PTO Ex. 1 ¶ 6.

13. Vasopressin has long been used in critical care situations to treat, among other things, dangerously low blood pressure for patients in septic shock and post-cardiotomy shock. Tr. 125:16-127:17 (Coralic); 494:7-496:10 (Cross).

14. Clinicians do not test the pH[1] of vasopressin products, or other intravenous drug products, prior to administering them to patients. Tr. 137:18-138:4, 144:16-19, 146:21-147:7 (Coralic). Rather, they administer such products to patients at whatever pH they happen to have at the time they are provided to the clinician for administration to a patient. Tr. 137:18-138:4, 144:16-19, 146:21-147:7 (Coralic).

15. Clinicians have and will administer vasopressin and other drug products at any time during the approved shelf-life of the drug product as long as it has been stored properly. Tr. 127:23-128:11 (Coralic), 504:5-8 (Cross).

[1] pH is a measure of the acidity of a solution and can affect the stability of drug molecules. Tr. 200:20-202:6 (Kirsch).

16. JHP Pharmaceuticals, LLC ("JHP") sold a vasopressin product under the tradename Pitressin for years prior to 2014.[2] DTX-0038.5; Tr. 390:16-391:5 (Park). Because vasopressin products were sold prior to adoption of the federal Food, Drug and Cosmetics Act, 21 U.S.C. ch. 9, § 301, *et seq.*, JHP was not required to obtain FDA-approval to make and sell Pitressin, and sold it as an unapproved drug product. DTX-0038.5; DTX-0025.9.

IV. PAR'S VASOSTRICT® PRODUCTS

A. Par's Original VASOSTRICT® Product

17. On September 25, 2012, JHP Pharmaceuticals, LLC submitted NDA No. 204485 under Section 505(b)(2) of the Federal Food, Drug, and Cosmetic Act, seeking approval from the FDA for a vasopressin injection product to increase blood pressure in adults with vasodilatory shock. PTO Ex. 1 ¶ 7.

18. On April 17, 2014, FDA approved NDA No. 204485. The trade name for the approved vasopressin product was VASOSTRICT®. PTO Ex. 1 ¶ 9.

19. The Vasostrict product as originally approved in April 2014 had a shelf-life of 12 months at room temperature storage. PTO Ex. 1 ¶ 10. Par never sold Vasostrict with the April 2014 Vasostrict Label that was approved at that

[2] On February 20, 2014, Par Pharmaceutical Companies, Inc. acquired JHP, and then on February 26, 2014, JHP changed its name to Par Sterile Products, LLC. PTO Ex. 1 ¶ 8.

time—i.e., with the 12 month room temperature shelf-life. *See* Tr. 719:2-7 (Kannan), 814:6-25 (Kirsch).

20. Par filed a supplement to its NDA (204485/S-001) seeking approval for storage between 2°C and 8°C and change in shelf-life expiration—to 24 months at refrigerated storage; FDA approved that supplement (NDA 204485/S-001) on September 18, 2014. PTO Ex. 1 ¶ 11. Vasostrict was first sold and offered for sale in November 2014, with the approved September 2014 label. PTO Ex. 1 ¶¶ 12, 16.

21. Par subsequently filed a second supplement to its NDA (204485/S-002) seeking approval for room temperature storage for up to 12 months following removal from storage at refrigerated conditions; FDA approved that supplement (NDA 204485/S-002) on May 7, 2015. PTO Ex. 1 ¶ 13.

22. Throughout the trial, the parties referred to the formulation as described in NDA 204485, and the supplements approved on April 17, 2014, September 18, 2014, and May 7, 2015 as "Original Vasostrict." PTO Ex. 1 ¶ 14.

23. As just described, there were three separate labels approved for Original Vasostrict, but Par only sold products under the latter two labels, both of which instructed refrigerated storage of the product. *See* above; *see also* Tr. 719:2-7 (Kannan), 814:6-25 (Kirsch); DTX-46.4; DTX-132.5.

24. Original Vasostrict was indicated to increase blood pressure in adults with vasodilatory shock (e.g., post-cardiotomy or sepsis) who remain hypotensive despite fluids and catecholamines. PTO Ex. 1 ¶ 15.

25. In accordance with the instructions on its label, Vasostrict is typically stored in a refrigerator under refrigerated conditions. Tr. 128:12-22 (Coralic), 504:9-11 (Cross). Hospital pharmacists will usually keep vasopressin refrigerated until it needs to be pulled from refrigeration for distribution throughout the hospital and administration to the patient. Tr. 128:12-22 (Coralic). This reflects a change from the prior use of vasopressin products, which were stored at room temperature. Tr. 143:1-12 (Coralic).

B. Par's Reformulated VASOSTRICT® Product

26. After Vasostrict was originally approved with a 12-month room temperature shelf-life, in addition to seeking a longer shelf-life under refrigerated conditions, Par also undertook a project to reformulate Vasostrict to obtain a more stable product that could support a longer room temperature shelf-life. *See, e.g.*, DTDX-2 (Kannan 2019 Tr.) 54:8-54:20, 70:14-71:2, 156:15-157:5; DTDX-8 (Vandse 2020 Tr.) 181:12-182:12; Tr. 714:10-23 (Kannan). Through their research efforts, the Par inventors determined that the pH 3.7-3.9 range achieved stability advantages that were unexpected in view of the prior art. *See, e.g.*, DTDX-4 (Kenney 2020 Tr.) 214:19-22, 215:9-15, 215:18-216:11; DTX-1115.14;

DTDX-8 (Vandse 2020 Tr.) 181:12-182:12, 182:18-182:23, 183:7-14, 185:21-25, 186:2-188:6; DTDX-10 (Sanghvi 2020 Tr.) 115:25-116:1, 116:4-5, 116:10-16; DTDX-7 (Vandse 2019 Tr.) 152:20-153:15; DTDX-3 (Kenney 2019 Tr.) 218:23-219:8, 219:10-12; DTDX-9 (Sanghvi 2019 Tr.) 152:10-18; Tr. 827:10-13 (Kirsch).

27. Based on that work, Par Sterile Products filed a further supplement to its NDA (204485/S-003) seeking approval for a new 1 mL formulation of Vasostrict. Changes to the formulation of Vasostrict in this supplement included addition of a sodium acetate buffer and a change in pH—from 3.4 to 3.6 in Original Vasostrict to 3.8 in Reformulated Vasostrict. On March 18, 2016, FDA approved NDA 204485/S-003. PTO Ex. 1 ¶ 17.

28. The data obtained by Par for Reformulated Vasostrict showed improvements as compared to Original Vasostrict, in terms of both higher vasopressin assay values and lower impurity levels. *See, e.g.*, DTDX-3 (Kenney 2019 Tr.) 89:8-13, 16-18, 20-21; DTDX-4 (Kenney 2020 Tr.) 217:3-17, 19-21, 219:19-24, 220:20-221:7; DTDX-7 (Vandse 2019 Tr.) 152:20-153:15, 251:22-252:6; DTDX-8 (Vandse 2020 Tr.) 181:12-182:12; Tr. 797:12-799:19 (Kirsch).

29. Moreover, Par obtained data sufficient to support an 18-month room temperature shelf-life for Reformulated Vasostrict, which was longer than the shelf-life that could be supported for Original Vasostrict. *See, e.g.*, DTDX-2 (Kannan 2019 Tr.) 235:18-22, 235:24-236:5, 297:9-298:5, 298:8-298:13; DTDX-3

(Kenney 2019 Tr.) 87:15-88:5; DTDX-4 (Kenney 2020 Tr.) 154:14-15, 154:17-25, 217:3-17, 217:19-21, 219:19-24, 220:20-221:7; DTDX-8 (Vandse 2020 Tr.) 181:12-182:12; Tr. 799:20-800:4, 888:5-17 (Kirsch); DTX-53.0016; PTX-252 at PAR-VASO_0030582.

30. Par Sterile Products also filed an additional supplement to its NDA (204485/S-004) seeking approval for a 10 mL multi-dose formulation of Vasostrict with the same concentration of vasopressin as the 1 mL formulation (i.e., 20 units of vasopressin/mL). On December 17, 2016, FDA approved NDA 204485/S-004. PTO Ex. 1 ¶ 18.

31. The parties refer to the current formulation of Vasostrict—approved on March 18, 2016 and December 17, 2016—as "Reformulated Vasostrict." PTO Ex. 1 ¶ 19.

32. The approved label for Reformulated Vasostrict discloses that it "is a sterile, aqueous solution of synthetic arginine vasopressin for intravenous administration. The 1 mL solution contains vasopressin 20 units/mL, Water for Injection, USP and, sodium acetate buffer adjusted to a pH of 3.8." PTO Ex. 1 ¶ 20.

33. Par first sold Reformulated Vasostrict in September 2016. PTO Ex. 1 ¶ 22.

34. Par Sterile Products is the holder of NDA No. 204485 for Vasostrict, including all supplements thereto. PTO Ex. 1 ¶ 24.

V. THE PATENTS-IN-SUIT

35. Par obtained patents[3] based on the above-described research and development work it performed in connection with the development of Reformulated Vasostrict, including: (1) U.S. Patent No. 9,750,785 (the "'785 Patent"), and (2) U.S. Patent No. 9,744,209 (the "'209 Patent") (collectively the "Asserted Patents"). JTX-002 ('209 patent); JTX-003 ('785 patent); Tr. 766:18-767:4, 775:16-776:10, 837:1-22, 838:20-840:9 (Kirsch).

36. The parties agree that the effective filing date of the '209 and '785 patents is February 7, 2017. PTO Ex. 1 ¶¶ 27, 29.

A. The '785 Patent

37. Par asserts claims 1, 5 and 8 of the '785 Patent, each of which is directed to specified vasopressin compositions. JTX-003.

38. In particular, the asserted claims of the '785 patent recite the following:

> **Claim 1**: A pharmaceutical composition comprising, in a unit dosage form, from about 0.01 mg/mL to about 0.07 mg/mL of vasopressin or a pharmaceutically-acceptable salt thereof, wherein the unit dosage form further comprises impurities that are present

[3] Par Pharmaceutical is the assignee and owner of the '209 and '785 patents. EPIC is the exclusive licensee of the '209 and '785 patents. PTO Ex. 1 ¶ 31.

in an amount of 0.9% to 1.7%, wherein the impurities have from about 85% to about 100% sequence homology to SEQ ID NO.: 1, and wherein the unit dosage form has a pH of 3.7-3.9.

Claim 5: The pharmaceutical composition of claim 1, wherein the impurities comprise SEQ ID NO.: 4, and SEQ ID NO.: 4 is present inthe unit dosage form in an amount of 0.2% to 0.4%.

Claim 8: The pharmaceutical composition of claim 1, wherein the impurities comprise SEQ ID NO.: 2 and SEQ ID NO.: 4, and SEQ ID NO.: 2 is present in the unit dosage form in an amount of 0.1% to 0.3% and SEQ ID NO.: 4 is present in the unit dosage form in an amount of 0.2% to 0.4%.

JTX-003.

B. The ’209 Patent

39. Par asserts claims 1, 4, 5 and 7 of the ’209 Patent, each of which is directed to methods of treatment using specified vasopressin compositions. JTX-002.

40. In particular, the asserted claims of the ’209 patent recite the following:

Claim 1: A method of increasing blood pressure in a human in need thereof, the method comprising administering to the human a unit dosage form, wherein the unit dosage form comprises from about 0.01 mg/mL to about 0.07 mg/mL of vasopressin or a pharmaceutically acceptable salt thereof, wherein:

the unit dosage form has a pH of 3.7-3.9;

the unit dosage form further comprises impurities that are present in an amount of 0.9% - 1.7%, wherein the impurities have from about 85% to about 100% sequence homology to SEQ ID NO.: 1;

the administration provides to the human from about 0.01 units of vasopressin or the pharmaceutically-acceptable salt thereof per minute to about 0.1 units of vasopressin or the pharmaceutically-acceptable salt thereof per minute; and

the human is hypotensive.

Claim 4: The method of claim 1, wherein the impurities comprise SEQ ID NO.: 4, and SEQ ID NO.: 4 is present in the unit dosage form in an amount of 0.2% to 0.4%.

Claim 5: The method of claim 1, wherein the impurities comprise SEQ ID NO.: 7, and SEQ ID NO.: 7 is present in the unit dosage form in an amount of 0.3% to 0.6%.

Claim 7: The method of claim 1, wherein the impurities comprise SEQ ID NO.: 2 and SEQ ID NO.: 4, and SEQ ID NO.: 2 is present in the unit dosage form in an amount of 0.1% to 0.3% and SEQ ID NO.: 4 is present in the unit dosage form in an amount of 0.2% to 0.4%.

JTX-002.

VI. THE COURT'S CLAIM CONSTRUCTIONS

41. The parties stipulated that the claim term "vasopressin" should be construed to mean "arginine vasopressin as described in SEQ. ID. NO. 1 (*see, e.g.*, '239 patent, cols. 25-26)" with respect to each of the Asserted Patents. D.I. 61 at 12; *see also* PTO Ex. 1 ¶ 54.

42. The Court ordered that the '209 patent claim term "administering to the human a unit dosage form" be given its "[p]lain and ordinary meaning; no construction necessary." D.I. 71.

43. No other claim term of the Asserted Patents was construed by the Court in Par's case against Eagle. PTO Ex. 1 ¶ 55

VII. PERSON HAVING ORDINARY SKILL IN THE ART ("POSA")

44. The parties' respective experts (Drs. Kirsch and Park) provided competing proposals concerning the definition of a person of ordinary skill in the art to which the Asserted Patents are directed ("POSA") that they acknowledge are very similar. *See, e.g.*, Tr. 211:19-212:1 (Dr. Kirsch testifying that using Defendants' definition of POSA would not affect his opinions), 388:20-389:1 (Dr. Park testifying that his and Dr. Kirsch's definitions are "not that different"). Their respective proposals are as follows:

- Par's Proposal: A POSA would have a Master's, Pharm.D., or Ph.D. in the field of pharmaceutical sciences or a related discipline and several years of experience in the development of pharmaceutical dosage forms. A person of ordinary skill in the art may also have less formal education and a greater among of experience. Further, a POSA would have had access to and would have worked in collaboration with persons who have several years of experience in the formulation of drug products as well as other professionals in the drug development field, such as pharmacologists, chemists, biologists, or clinicians. Tr. 210:22-211:14 (Dr. Kirsch's definition);

- Defendants' Proposal: A person of ordinary skill in the art is someone who has a master's degree, or a PhD degree in pharmaceutical sciences or related skill with several years of experience in development pharmaceutical dosage forms, including stable aqueous peptide formulations and more experience may substitute for lower level of education and vice-versa. Also, a person can have access to and collaboration with persons having drug formulation experience, as well as pharmacologists, chemists, biologists or clinicians. Basically, can work as a team. Tr. 388:5-19 (Dr. Park's definition).

45. Both side's experts testified that their opinions would not change if the Court were to adopt the other side's definition. Tr. 388:20-389:1 (Park); 211:19-212:1, 827:14-25 (Kirsch). Therefore, the Court need not make an express finding as to which party's definition of a POSA it will use.

VIII. EAGLE'S ANDA PRODUCT

A. Background

46. On January 25, 2018, Eagle submitted ANDA No. 211538 ("Eagle's ANDA") pursuant to 35 U.S.C. § 355(j), seeking approval to engage in the commercial manufacture, use, and sale of a proposed generic vasopressin product, Vasopressin Injection USP, 20 units/1 mL ("Eagle's Proposed ANDA Product"), identifying Vasostrict as the reference listed drug. PTO Ex. 1 ¶ 39; *see* DTX-0133.001.

47. Eagle's ANDA includes Paragraph IV certifications to the Asserted Patents, certifying that Eagle believes the Asserted Patents are invalid or will not be infringed by the commercial manufacture, use, or sale of Eagle's Proposed ANDA Product. PTO Ex. 1 ¶ 41.

48. While "Eagle specifie[d] the original version of Vasostrict®, approved April 17, 2014, as the RLD" per a waiver under 21 C.F.R. § 314.99(b) (DTX-131.1; Tr. 346:21-347:4, 348:5-20 (Park)), Eagle conducted comparative

studies of its product against Reformulated Vasostrict to support approval of its ANDA. *See, e.g.,* DTX-133.0034, 0036; Tr. 479:3-481:18 (Park).

49. Pursuant to its ANDA, Eagle is seeking FDA approval to make, use, and sell its Proposed ANDA Product before expiration of the Asserted Patents. PTO Ex. 1 ¶ 40.

50. If approved, Eagle's Proposed ANDA Product would, when sold, be packaged together with a package insert (also commonly referred to as the "label"), the current proposed draft of which is PTX-1417, along with carton labeling (PTX-1419) and vial labeling (PTX-1420). PTO, Ex. 1 ¶ 52; Tr. 129:8-22, 133:18-134:5 (Coralic).

51. Eagle's package insert/label describes that the product "is adjusted with acetic acid to pH 3.4-3.6." PTX-1417, at EAGLEVAS0060906. The "adjusted … to" language refers to adjustments made by the manufacturer during the manufacturing process (i.e., prior to its release for sale). *See* Tr. 64:6-65:4 (colloquy); 256:5-257:10 (Kirsch).

52. Eagle's Proposed ANDA Product seeks the same shelf-life and storage conditions as Vasostrict. Tr. 134:16-21 (Coralic); PTX-1422 at EAGLEVAS0061162-63.

53. If approved by FDA, Eagle's ANDA products, like other drug products, could be administered any time during their approved shelf-life. Tr. 127:23-128:11 (Coralic), 504:5-8 (Cross).

B. Eagle's Vasopressin Batches

54. Eagle, through its joint venture partner AMRI, has manufactured a total 17 batches of Eagle's Proposed ANDA product (SVA001-017). PTO Ex. 1 ¶ 44; PTX-1443 (Aungst 2021 Tr.) 20:19-22. Batches 10 and 15 were rejected for reasons unrelated to any disputed issues in the case, and therefore no pH data or stability data on those batches was presented at trial. Tr. 354:7-19 (Park); *see generally* DTX-993; DDX7-1.

1. Eagle's "Registration Batches" (SVA001-003)

55. Batches SVA001-003 are referred to as the "registration batches." *See, e.g.*, PTX-1435, at 4. Registration batches (sometimes also referred to as exhibit batches) are batches manufactured to evaluate the stability of the product and its attributes in comparison to the RLD and are used to generate data contained in the ANDA. DTDX-1, (Aungst 2019 Dep. Tr.) 85:21-86:5; Tr. 220:19-221:3 (Kirsch); 351:8-19 (Park).

56. Eagle has completed its stability protocol for its registration batches and has reported 24-month pH data to the FDA for those batches. *See*, *e.g.*, PTX-1435, at 9; DTX-993.001.

57. As discussed in more detail below, data generated on Eagle's registration batches revealed that the pH of the product would drift upward over time while stored in refrigerated conditions. PTX-1435, 9-10.

2. Eagle's "Characterization Batches" (SVA004-006)

58. Eagle and AMRI manufactured three additional batches, which it calls "characterization batches," in accordance with the manufacturing process used for the registration batches. PTO Ex. 1 ¶¶ 46-47; DTX-331.0020.

59. Eagle made them in order to generate stability data under "worst-case RLD label storage of 12 months 2-8°C plus 12 months 25°C/60%RH," and "to provide product samples at or near release for proper characterization of the drug product." PTX-1435, at 20.

60. Eagle has completed its stability protocol for its characterization batches and has reported 24-month pH data to the FDA for those batches. *See*, *e.g.*, PTX-1435, at 23; DTX-993.001.

3. Eagle's "Optimization/Confirmation Batches" (SVA007-009)

61. Eagle and AMRI thereafter made an additional three "optimization/confirmation batches." PTO Ex. 1 ¶ 48.

62. As discussed in more detail below, Eagle manufactured its optimization/confirmation batches in order to test changes to the manufacturing process and in-process specifications that Eagle made in response to out-of-

specification data obtained on the registration batches. PTX-1435, at 25; Tr. 352:23-353:4 (Park).

63. Eagle has not completed its stability protocol for its optimization/confirmation batches and has reported only 18-month pH data to the FDA for those batches. *See*, *e.g.*, PTX-1435, at 27; DTX-993.001; Tr. 359:25-360:2 (Park).

4. Eagle's Process Performance Qualification ("PPQ") Batches (SVA011-013)

64. Eagle and AMRI subsequently manufactured batches SVA011-13 in November and December of 2020, which are referred to as "PPQ" batches because they were used in process performance qualification studies that are described in more detail below. Tr. 353:5-7 (Park); PTX-1443 (Aungst 2021 Tr.) 21:01-21:10. Eagle and AMRI manufactured the PPQ batches in accordance with Eagle's currently-proposed commercial manufacturing process. Tr. 353:5-17 (Park); PTX-1443 (Aungst 2021 Tr.) 21:08-10; 21:12-18.

65. The PPQ batches have six-months of stability pH testing data available. DDX7-1; DTX-993; Tr. 360:3-5 (Park).

66. Eagle has not submitted any pH data from the PPQ batches to FDA. Tr. 240:6-10 (Kirsch); *see,* PTX-1435 (reporting on data for only batches SVA001-009).

5. Eagle's Additional Batches SVA014, 016, 017

67. After manufacturing the PPQ batches, Eagle and AMRI manufactured batches SVA014, 016, 017 in accordance with Eagle's currently-proposed commercial manufacturing process. Tr. 351:8-353:17 (Dr. Park noting that batches SVA007 and up are representative of the pH of Eagle's commercial product).

68. Batches SVA014, 016, and 017, were not placed in a stability protocol. Tr. 354:7-10 (Park). Accordingly, no pH data after release was presented for these batches at trial. *Id*.; *see* DTX-993; DDX7-1.

69. Eagle has not submitted any pH data from batches SVA014, 016, or 017 (or any batches after SVA009) to FDA. Tr. 240:6-10 (Kirsch); *see,* PTX-1435 (reporting on data for only batches SVA001-009).

C. Eagle's pH Testing and Specifications

70. As described herein, Eagle conducts pH testing at various stages during the life of a batch including: (1) during compounding, (2) during in-process testing, (3) during release testing, and (4) during stability testing for batches subject to a stability protocol, and Eagle additionally conducted non-routine testing on batches SVA011-013 per its Process Performance Qualification ("PPQ") Protocol.

71. When Eagle tests and reports the pH of its product after the bulk solution has been filled into individual vials (i.e., for the final in-process testing,

release testing, and stability testing), each pH test is conducted on a pooled sample of five vials. Tr. 217:8-218:3 (Kirsch); 370:20-371:7, 382:2-18 (Park). Moreover, when Eagle reports pH measurements, it rounds the measured values to the level of precision set forth in the specification. *See* Tr. 226:2-227:1 (Kirsch); PTX-1435, at 9 ("The pH results of 3.35 and 3.64 represent the lower and upper bounds of the pH specification of 3.4 to 3.6."); PTX-1443 (Aungst 2021 Tr.) 47:25-49:08. The use of rounding to report pH measurements is common practice to POSAs. Tr. 210:2-21 (Kirsch).

1. Compounding pH Measurements and Adjustments

72. Eagle tests the pH of its batches during a part of the manufacturing process called "compounding," which is the process of combining, mixing, or altering ingredients to create a medication. Tr. 363:1-7 (Park); D.I. 276, at 3; D.I. 277, at 1.

73. Eagle set forth the compounding steps for its registration batches and characterization batches[4], including the pH adjustment and measurement steps, in Figure 1 of DTX-323. DTX-323.0005.

74. After manufacturing the registration and characterization batches, Eagle and AMRI "slightly modified" their manufacturing process for the

[4] The same compounding process was used for Eagle's characterization batches. PTO Ex. 1 ¶ 47.

optimization/confirmation batches, as well as proposed commercial batches. DTDX-1 (Aungst 2019 Tr.) 81:20-24; 86:21-87:11. These manufacturing changes were aimed at achieving "some slight changes in terms of the pH within the overall product at the time of release." DTDX-1, (Aungst 2019 Tr.) 86:21-87:11; *see also* PTX-1435, at 9. Eagle's "optimized" manufacturing process is set forth in Figure 4 of DTX-323. DTX-323.0016.

2. In-Process pH Testing

75. In-process specifications are, in-part, designed to assure that the final product will meet its quality requirements, and are intended to be consistent with the drug product's final specifications. *See* D.I. 276, at 2-3.

76. Eagle's in-process pH tests refer to a pH measurement of the bulk solution prior to microbial filtration (e.g., the "pre-filtration" test results) and a pH measurement conducted on a pooled sample of 5 vials selected from the first 300 vials filled after filtration to remove microbial contamination (e.g., the "post-filtration" test results). *See, e.g.*, Tr. 242:21-243:20 (Kirsch).

77. Eagle's in-process pH specifications fluctuated between its registration batches, process optimization/confirmation batches, and intended commercial batches as shown in Table 3 of DTX-323:

Table 3: Registration, Process Optimization/ Confirmation, and Intended Commercial Batch In-Process Parameters

Stage	In-Process Parameter	Registration Batches	Process Optimization/ Confirmation Batches	Intended Commercial Production Batches
Equipment & Stopper Sterilization	Sterilization Conditions	Sterilization time 19 to 21 minutes for equipment & 29 to 31 minutes for stoppers. Temperature during sterilization 121°C to 124°C	Sterilization time 19 to 21 minutes for equipment & 29 to 31 minutes for stoppers. Temperature during sterilization 121°C to 124°C	Sterilization time 19 to 21 minutes for equipment & 29 to 31 minutes for stoppers. Temperature during sterilization 121°C to 124°C
Compounding	pH of Chlorobutanol/ Acetic Acid/ WFI solution	NA[1]	3.0 – 5.0[1]	3.0 – 4.0
	Relative Humidity in Glove Bag (for API Handling/ Dispensing)	NA[1]	NMT 10% RH	NMT 10% RH
	Pre-QS Assay Vassopressin	NA[1]	Report Result (used to determine QS requirement)	Report Result (used to determine QS requirement)
	Appearance	Clear, colorless, to practically colorless solution, essentially free of visible particulates	Clear, colorless, to practically colorless solution, essentially free of visible particulates	Clear, colorless, to practically colorless solution, essentially free of visible particulates
	pH	2.5 – 4.5 (Target 3.4 – 3.6)	3.42 – 3.50	3.42 – 3.54
Filtration	Filtration Pressure	NMT 25 psig (filtered Nitrogen, NF)	NMT 25 psig (filtered Nitrogen, NF)	NMT 25 psig (filtered Nitrogen, NF)
	Bubble Point Value (before & after filtration)	NLT 46 psig (rinse with WFI)	NLT 46 psig (rinse with WFI)	NLT 46 psig (rinse with WFI)
Post-Filtration	Appearance	Clear, colorless, to practically colorless solution, essentially free of visible particulates	Clear, colorless, to practically colorless solution, essentially free of visible particulates	Clear, colorless, to practically colorless solution, essentially free of visible particulates
	pH	2.5 – 4.5 (Target 3.4 – 3.6)	3.42 – 3.50	3.42 – 3.54

DTX-323.0012-13.

78. As can be seen in Table 3, Eagle broadened the upper limit of its in-process pH specification, from 3.50 to 3.54, after manufacturing the optimization/confirmation batches (SVA007-009). *Id*.; *see* Tr. 469:5-471:4 (Park).

79. None of Eagle's optimization/confirmation batches or subsequent batches have been manufactured at the upper limit (i.e. 3.54) of Eagle's current in-process, post-filtration, pH specification. *See, e.g.*, DTX-993.0013; DDX7-1.

3. Release pH Testing

80. Release specifications are "[t]he combination of physical, chemical biological, and microbiological tests and acceptance criteria that determine the suitability of a drug product at the time of its release." D.I. 276, at 2; *see* Tr. 349:15-17 (Park). "For each batch of drug product, there shall be appropriate laboratory determination of satisfactory conformance to final specifications for the drug product…prior to release" and products that fail to meet the release specifications "shall be rejected." 21 C.F.R. 211.165(a), (f). The converse is also true—drug products meeting those specifications may be released for commercial sale. *Id*.; *see* D.I. 277; Tr. 219:18-21 (Kirsch); Tr. 412:20-413:3 (Park). The release pH test is conducted once the filling operation is complete. Tr. 219:13-17 (Kirsch).

81. The release pH specification in Eagle's ANDA has remained constant at 3.4-3.6 since Eagle submitted its ANDA. *See, e.g.* Tr. 349:8-350:16 (Park); DTX-327.1; DTX-678.2; PTX-1427 at 1.[5]

82. Eagle conducts release testing by pooling five vials randomly selected from the over 25,000 vials that make up the batch. Tr. 217:4-218:3 (Kirsch); PTX-1443 (Aungst 2021 Tr.) 41:04-42:02.

83. At trial, Eagle and AMRI's representative (Dr. Aungst) gave equivocal and somewhat contradictory evidence about whether Eagle would be authorized to release and sell a batch that was above the in-process pH specification but thereafter met the release pH specification at the time of release testing.[6] There was no dispute at trial, however, that Eagle can and will release and sell batches that meet Eagle's in-process and release pH specifications. *See, e.g.*, Tr. 471:18-23 (Park).

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[5] When AMRI first manufactured its registration batches (which was before its partnership with Eagle, (Tr. 261:14-18, 262:4-15 (Kirsch)) it listed broader pH ranges of 2.5 to 4.5 for the release and stability pH specifications. Tr. 263:17-21 (Kirsch); 375:15-23 (Park). As just noted, however, by the time Eagle prepared and submitted its ANDA, the release specification had been narrowed to 3.4-3.6. Each of the registration batches had a pH upon release that was within that range, with SVA001 at the very top end of it (pH 3.64). DTX-993.0001; DDX7-1.

[6] For example, compare DTDX-1, (Aungst 2019 Tr.) 110:6-17 and 113:13-114:4 (indicating that Eagle could release such a batch, or that Dr. Aungst did not know whether it could), with 109:16-110:4 and 111:2-112:8 (indicating that AMRI would not release such a batch).

4. Stability pH Testing

84. Stability specifications are the combination of physical, chemical, biological, and microbiological tests and acceptance criteria that a drug product should meet throughout its shelf-life. *See* D.I. 276, at 2; Tr. 349:18-20 (Park); 21 C.F.R. §§ 211.166-.167, .170.

85. Upon FDA approval Eagle will place its first three commercial batches into a stability protocol, followed by one batch on stability every year after that. Tr. 220:2-12 (Kirsch). Of the few batches that are placed on stability, only a small percentage of the over 25,000 vials will ever be tested for pH. Tr. 220:13-18 (Kirsch).

86. Eagle's current stability pH specification is the same as its release pH specification, 3.4-3.6. *See* PTX-1427.

5. Process Performance Qualification ("PPQ") pH Testing

87. Eagle and AMRI manufactured batches SVA011-013 per Eagle's proposed commercial manufacturing process (i.e. its "optimized" process) for the purpose of PPQ studies. PTX-1443 (Aungst 2021 Tr.) 21:01-21:10, 21:12-18. PPQ studies are used to validate the overall manufacturing process, in which the manufacturer "test[s] various portions of the batch manufacture that are not typically tested on a routine basis." PTX-1443 (Aungst 2021 Tr.) 26:03-26:19.

88. Eagle and AMRI's PPQ protocol included four tests. PTX-1235, at AMRIVAS0118387; PTX-1443 (Aungst 2021 Tr.) 35:13-22. One of the tests, denominated test function #3, was conducted in order to "verify the uniformity of the SVA finished product and to ensure it meets final product specifications over the entire fill." PTX-1235, at AMRIVAS0118399; PTX-1443 (Aungst 2021 Tr.) 35:23-36:11. In other words, AMRI tested the attributes of its finished drug product (vials) from various stages of the filling process to determine whether product attributes were affected by the length of the filling process. PTX-1443 (Aungst 2021 Tr.) 36:15-18; 36:21-37:02; 37:07-37:17.

89. Accordingly, AMRI segregated vials from the beginning of the filling process, middle of the filling process, and end of the filling process, and tested those vials to determine whether vials filled during the different stages in the filling process had the same attributes. PTX-1443 (Aungst 2021 Tr.) 37:07-37:17; 39:03-39:10.

90. AMRI and Eagle intended the release pH for the PPQ batches to be determined by using an average of the pH measurements conducted on beginning, middle, and end vials as set forth in test function 3 of the PPQ protocol. PTX-1443 (Aungst 2021 Tr.) 41:04-12.

91. AMRI conducted in-process pH testing on batch SVA011 and measured values of 3.50 for both the pre-filtration and post-filtration tests. PTX-1353, at AMRIVAS0120375, 77; DTX-993.0013; DDX7-1.

92. On November 30, 2020, an AMRI chemist named Tamara Smith conducted release pH testing per test function 3 of the PPQ protocol for vials collected from SVA011 and recorded values of 3.54, 3.56, and 3.57. PTX-1217; PTX-1443 (Aungst 2021 Tr.) 45:20-23; 46:04-46:09; 47:25-49:05; 49:07-08; 49:10-13; 49:16-20; 87:14-19.

93. On December 2, 2020, another AMRI chemist named Tania Espina inadvertently repeated the test function 3 release pH testing for SVA011 and separately recorded values of 3.51, 3.49, and 3.47. PTX-1344, at AMRIVAS0120364; PTX-1443 (Aungst 2021 Tr.) 54:09-54:12; 56:08-56:13; 56:19-56:23; 58:02-59:12; 87:20-23.

94. Upon learning that it had inadvertently repeated the test function 3 release pH testing for SVA011, AMRI decided to report all six pH results obtained since they were all valid measurements. In other words, none of the pH tests conducted by Ms. Smith or Ms. Espina had "lab error" and that "[a]ll indications were they were accurate results." PTX-1443 (Aungst 2021 Tr.) 87:14-89:17. Accordingly, AMRI elected to utilize all the data, and all six values are now listed

in the end-product lab notebook. PTX-1321, at AMRIVAS0120366; PTX-1443 (Aungst 2021 Tr.) 87:14-89:17.

95. SVA011 is the only batch that has had six release tests conducted on it. *See, e.g.*, DDX7-1.

IX. EAGLE'S PRODUCTS DRIFT UPWARD WHEN STORED IN REFRIGERATED CONDITIONS

A. The pH of Eagle's Registration Batches Drifted Upward Under Refrigerated Conditions

96. As discussed above, Eagle seeks the same shelf-life and storage conditions for its ANDA product as Vasostrict. Tr. 134:16-21 (Coralic); PTX-1422, at EAGLEVAS0061162-63. That is a shelf-life of "24 months at a storage temperature of 2–8°C," and allowance for storage at 25°C "for a period of 12 months after removal from 2–8°C, not to exceed the original assigned expiry period." *See, e.g.*, *id.*; PTX-1417, at EAGLEVAS0060909; PTX-1435, at 30; PTO Ex. 1 ¶ 43.

97. Like Vasostrict's label, Eagle's label instructs pharmacists to store Eagle's ANDA product in refrigerated conditions. PTX-1417, at EAGLEVAS0060909 ("Store between 2°C and 8°C (36°F and 46°F").

98. The 24-month pH test of SVA001 when stored upright and in refrigeration measured values of 3.7, 3.8, and 3.7. PTX-208, at EAGLEVAS0047273; Tr. 220:19-23, 221:15-222:8 (Kirsch). Eagle reported three

pH results because the original measurement of 3.69 was out of specification. Tr. 357:11-358:2 (Park); DTX-993.0001, 0013. This prompted a retest of the same pooled sample of five vials that was measured at 3.75. *Id*. At that point, the operator pooled a new sample of five vials and measured the pH to be 3.68. *Id*.

99. The out-of-specification ("OOS") pH results for SVA001 prompted an investigation by AMRI that was documented in a report identified as PR661354. Tr. 224:4-225:16 (Kirsch); PTX-53. In the OOS report PR661354, AMRI ruled out analytical error or other error that could have caused the OOS pH results for SVA001. Tr. 224:19-225:10 (Kirsch); PTX-53, at AMRIVAS0114547. AMRI concluded that "[t]he product is the likely root cause of the high pH." PTX-53, at AMRIVAS0011458; Tr. 224:4-225:16 (Kirsch); DTDX-1 (Aungst 2019 Tr.) 273:16-275:4.

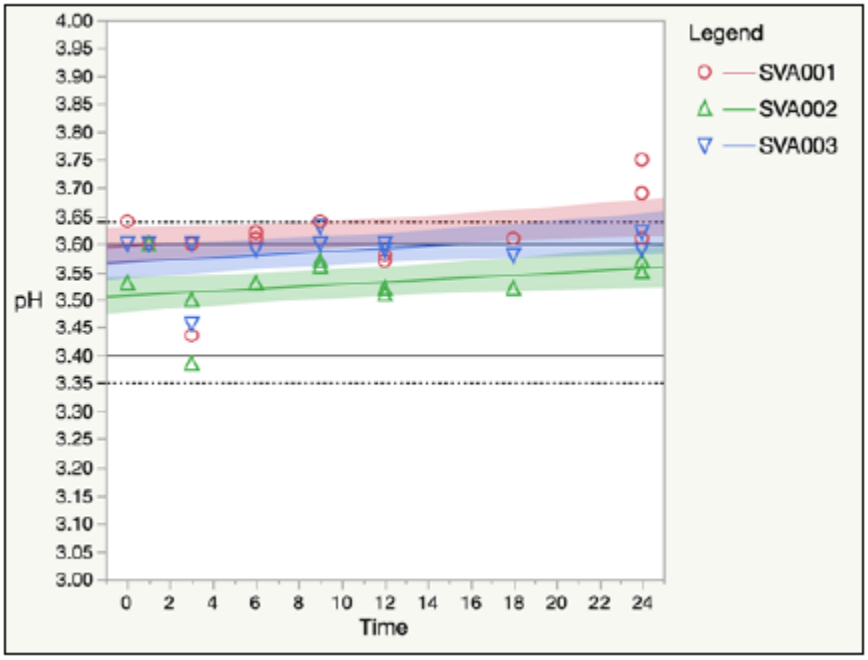
100. Eagle reported the pH results for SVA001 to FDA in its Module 3.2.P.8.1 Stability Summary and Conclusion, which was recently updated in June 2021. Tr. 225:17-226:1 (Kirsch); PTX-1435. In this module, Eagle explained to FDA that the release pH for SVA001 was 3.64, which is the upper boundary of its release pH specification of 3.4-3.6. PTX-1435, at 9; Tr. 226:2-12 (Kirsch). With respect to the OOS pH results for SVA001, Eagle stated that "[t]he root cause of the OOS was determined to be batch SVA001 was released at the upper limit of the pH specification (the release value was 3.64, which rounds to 3.6)." PTX-1435, at

9; Tr. 227:2-16 (Kirsch); *see* DTDX-1 (Aungst 2019 Tr.) 226:12-226:25, 227:6-227:10; PTX-217, at EAGLEVAS0047336.

101. Eagle additionally submitted a statistical analysis of the pH data for its registration batches SVA001-003 when stored in refrigeration and concluded that the slopes were found statistically significant and slightly increasing over 24 months with a 12 month increase of 0.024 pH units. PTX-1435, at 9; Tr. 294:17-22 (Kirsch); *see* DTDX-1 (Aungst 2019 Tr.) 225:10-13, 225:25-226:11; PTX-217, at EAGLEVAS0047336.

102. Eagle submitted the below Fig. 1 to accompany its statistical analysis of SVA001-003 when stored in refrigeration:

Figure 1: pH Results for the Registration Batches at 2-8°C for 24 Months



PTX-1435, at 10.

103. Figure 1 plotted the pH data for SVA001-003 along with the trend line associated with the pH data for each batch and confidence intervals that show where the pH values would be expected to fall 95% of the time. Tr. 236:7-237:5, 317:24-318:13 (Kirsch). The data plotted in Figure 1 shows that the confidence interval Eagle calculated for the SVA001 pH values (the pink shaded area) included values of 3.65 or higher—i.e., within the claimed range of Par's patents—as early as 10 months. Tr. 236:7-237:5, 237:16-21, 319:18-320:7 (Kirsch). Similarly, the confidence interval Eagle calculated for the SVA003 pH values (the blue shaded area) included values within the claimed range of Par's patents beginning around 20 months. Tr. 237:16-238:13, 319:18-320:7 (Kirsch). SVA003 had a release value of 3.60. Tr. 238:14-17, 317:20-318:13 (Kirsch); DTX-993.0001; DDX7-1.

104. Eagle did not change its release pH specification of 3.4-3.6 after investigating the cause of the OOS pH results for SVA001 and conducting its statistical analysis of the pH data for batches SVA001-003. Tr. 223:17-23 (Kirsch); *see also S*ection VIII.C.3. Accordingly, if the FDA approves Eagle's ANDA as it stands currently, Eagle could release a commercial batch at the upper limit of the release pH specification. Tr. 235:24-236:2 (Kirsch), 471:18-23 (Park).

B. Eagle's Attempt to Solve the pH Problem

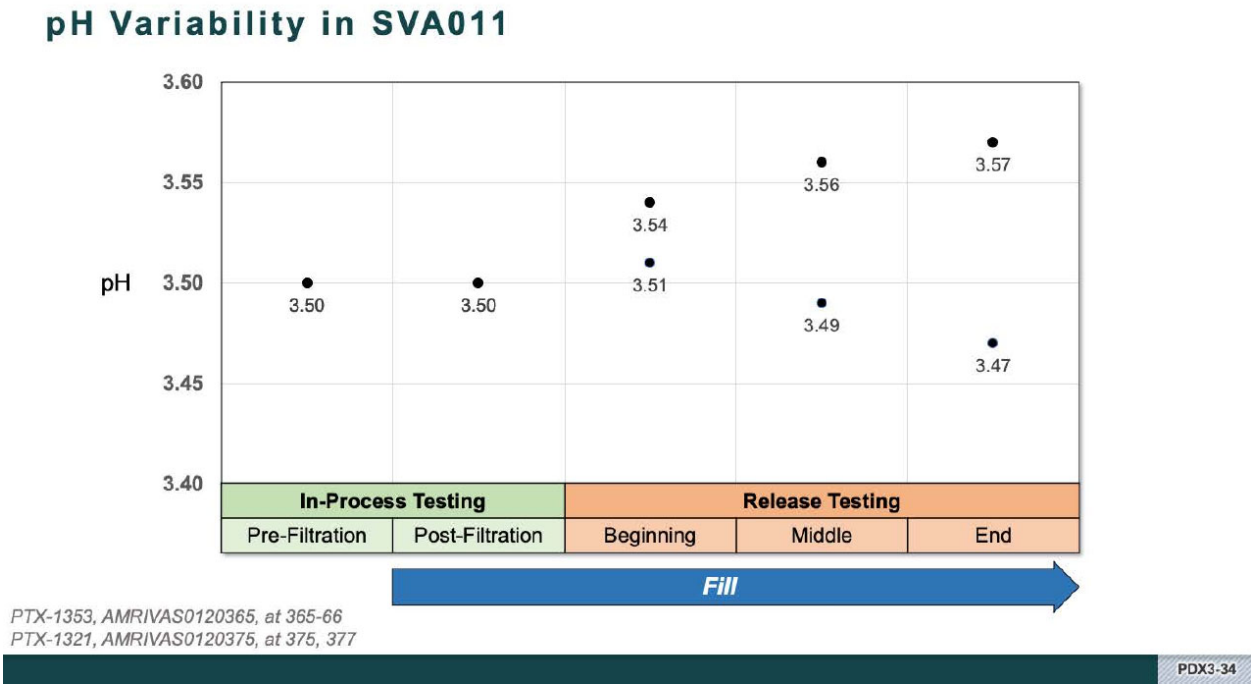
105. Instead of seeking to avoid infringement by lowering its release pH specification, thus binding itself to a value low enough to account for its product's upward drift and Par's patents, Eagle chose to attempt to "optimize" its manufacturing in-process controls "to assure tighter control of pH" during manufacturing. PTX-1435, at 9. Eagle reiterated this to FDA in its June 2021 submission. *Id.*; Tr. 225:17-226:1 (Kirsch).

106. These manufacturing changes were set forth in Module 3.2.P.3.3 as discussed above in Section VIII.C.1. *See* PTX-1435, at 10; DTX-323.0016. "Specifically, the pH adjustment steps in the batch record were optimized for better control of the batch pH to the middle of the pH specification (i.e. 3.50)." PTX-1435, at 25; Tr. 366:22-367:18, 372:14-373:1 (Dr. Park: the goal of Eagle's manufacturing changes is to achieve a "homogeneous" solution and to have a "narrower tighter pH reading.").

C. Eagle's "Optimizations" Failed to Solve Its Upward Drift Problem

107. The supposed "optimizations" did not achieve the goal of attaining a homogenous solution. As evidenced by the six release pH measurements for SVA011 of vials filled at nearly the same time (described in Section VIII.C.5), the pH continued to vary by as much as 0.1 pH units between sample vials pulled from

the beginning and end of the filling run. Dr. Kirsch presented the data on the following graph:



PDX3-34; Tr. 242:18-246:22 (Kirsch). Dr. Kirsch explained that the additional pH measurements for SVA011— that were not available for any other batch—provide a better sense of pH variability among vials filled from a single batch of Eagle's product than any other available data. Tr. 245:3-8 (Kirsch). He further opined that similar variability would be expected in other batches of Eagle's ANDA product. Tr. 244:20-245:2 (Kirsch).

108. Thus, this evidence on variability—which Eagle has not submitted to the FDA (*see, e.g.*, PTX-1435 (reporting on data for only batches SVA001-009))—

shows that Eagle's optimizations failed to achieve their goal. Tr. 240:6-246:21 (Kirsch).

109. The data derived from Eagle's stability testing of its "optimized" batches also demonstrates that even when Eagle uses its supposedly "optimized" manufacturing process (i.e., for batches SVA007-9, 11-14, 16-17), the pH of Eagle's ANDA product can drift upward significantly between the time of the final in-process (post-filtration) testing and release testing. DDX7-1; Tr. 244:6-19 (Kirsch), 460:12-461:12 (Park).

110. For example, the pH of SVA011 at the post-filtration in-process test was 3.50 yet had pH values upon release testing (reported as "initial") as high as 3.56 and 3.57—a 0.06 and 0.07 pH unit increase. DDX7-1, Tr. 244:6-19 (Kirsch), 460:12-24 (Park).[7] Similarly, the post-filtration in-process pH test for SVA012 was 3.44, yet it had pH values on release as high as 3.50—a 0.06 pH unit increase.

[7] Dr. Park testified that the goal of Eagle's optimizations was to achieve a "homogenous" solution with "a narrower tighter pH reading." Tr. 366:22-367:18 (Park). In order to test whether a "homogenous" solution with "narrower tighter pH reading[s]" was actually achieved, one would need to take multiple repeat pH measurements from vials filled at or near the same time. *See, e.g.*, Tr. 245:3-8; 246:3-8 (Kirsch). Dr. Kirsch explained that the best batch to assess whether the batches are in fact uniform is SVA011, because AMRI conducted six separate release pH tests on the batch. *Id*. However, instead of the pH values all measuring very close together, which one would expect if the batch were truly uniform, the pH values differed by as much as 0.1 pH units. Tr. 240:11-243:20 (Kirsch).

DDX7-1; Tr. 460:25-461:4 (Park). SVA008 also exhibited a 0.04 pH unit increase between the post-filtration in-process pH test and release. DDX7-1.

111. Eagle's expert Dr. Park agreed that 0.07 or 0.06 pH unit increases from post-filtration pH testing to release testing is "representative of" and could be expected of commercial batches:

> Q. Okay. So it's representative of the commercial batches to expect a difference in-process versus the release reading could be in the order of .07 or .06, because that's the data that we have now; is that correct?
>
> A. Yes.

Tr. 461:8-12. Given that Eagle's current in process specification would allow commercial manufacture at pH 3.54, adding 0.06 or 0.07 pH units to the in-process specification would result in a pH at release of 3.60 or 3.61, within the upper end of the release specification. Tr. 246:9-22 (Kirsch).

112. Upward drift was also observed following release. The only "optimized" batches that had pH stability data—SVA007-9, 11-13 (*see* Section VIII.B)—demonstrated significant post-release drift, oftentimes within the very first month thereafter.[8] Accordingly, Dr. Park agreed that the data from Eagle's

[8] At times, Eagle has taken the position that infringement must be measured at or around the time of manufacture, rather than during the shelf life. Eagle did not pursue that interpretation at trial, and indeed, the proper time for the argument was at claim construction. Now that the evidence is in though, it is plain that such a construction would have been of no help to Eagle. The real-world evidence shows significant drift right after release. Even with the very limited available data, the trial record shows upward pH drift of 0.04 units between release and the 1 month

stability studies on the optimized process showed an increase in pH from release through shelf life of as much as .06 pH units:

> Q. Yes. No, that's not my question. My question was here we showed it from release through product life. We saw increases of .05, .04, .04, .06, .04, .05 in the data that you say is representative of the batch between release and shelf life; correct?
>
> A: Yes.

Tr. 474:7-12.

113. Dr. Park confirmed other facts regarding post-release drift as well. He agreed that all but one "optimized" batch with available stability data experienced upward pH drift after release. PTX-1442; Tr. 450:17-455:16, 468:19-469:4 (Park). The data, confirmed by Dr. Park, shows that upward drift was as much as 0.06 pH units, with four of the six batches experiencing upward pH drift of at least 0.04 pH units while on stability. PTX-1442; Tr. 450:17-451:6, 452:2-3, 452:7-11, 452:24-454:10, 454:22-455:16, 468:19-469:4 (Park). Dr. Park also confirmed that there was as much as 0.04 pH units of upward pH drift within a month of release in some of the batches. *Id*.

114. The stability data is illustrated below on an annotated version of Eagle's DDX7-4. The cells with red boxes are pH measurements that exceed the

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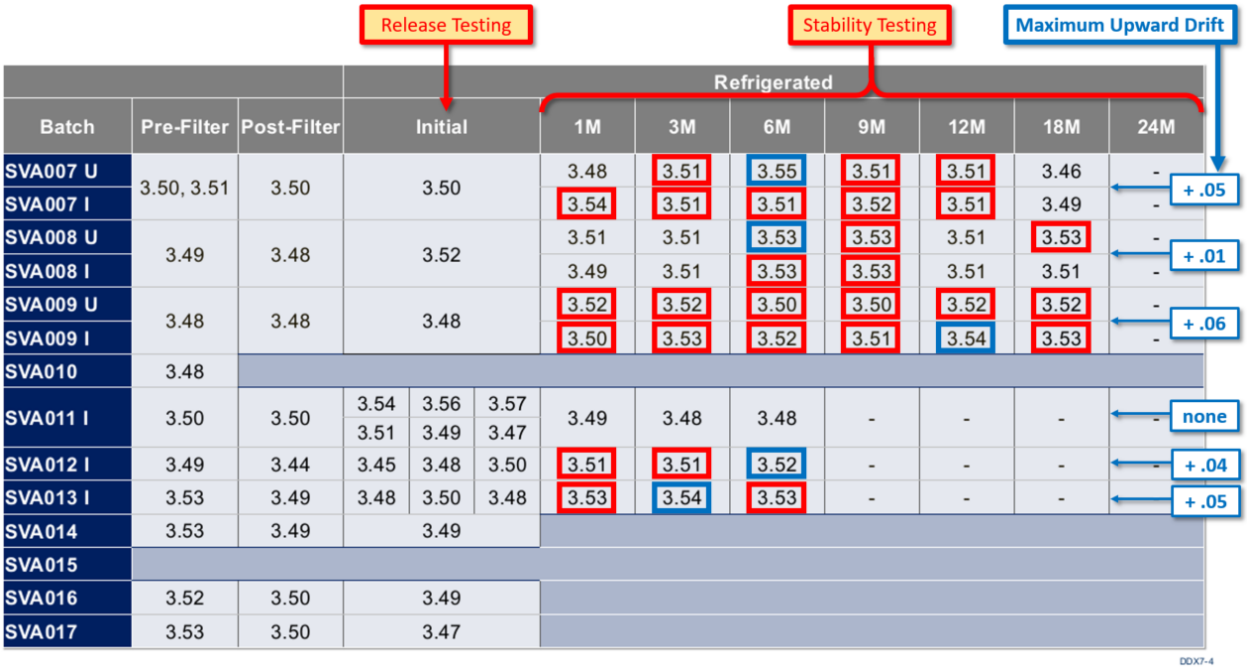
measurement, i.e. around the time of manufacture and before sale. Eagle cannot avoid infringement by making a product just short of the pH finish line and then letting it drift across the line after release.

release pH value for that particular batch.[9] The cells with blue boxes show the maximum drift above the release pH value for a particular batch:



As can be seen in the annotated demonstrative, Eagle took 45 pH measurements of its "optimized" batches after release while stored in refrigeration, and 32 of them drifted upward after release. Dr. Park confirmed that these increases are representative of an Eagle batch after release. Tr. 474:7-12 (Park); PTX-1442.

115. In summary, the data generated on Eagle's "optimized" batches shows that Eagle has not sufficiently controlled the pH of its product to prevent

[9] For PPQ batches SVA011-13 that have multiple release values, the average release value for each batch was used to illustrate the pH increase after release. The average release pH values for SVA011-13, were 3.52, 3.48, and 3.49 respectively. DTX-993.0001.

infringement of Par's patents. In particular, future batches manufactured at the upper limit of Eagle's post-filtration in-process pH specification (3.54), would be expected to have release values as much as 0.07 pH units higher (i.e., at least as high as pH 3.61) by the time of release testing, which would place the batch within the upper-end of the release pH specification. Tr. 245:9-246:22 (Kirsch), 461:8-12, 473:13-474:2, 474:7-18 (Park).

116. Moreover, the evidence from Eagle's registration batches demonstrates that batches released at the upper end of the release pH specification would be expected to have pH values between 3.7-3.9 during their shelf-lives. *See* Section IX.A. The "optimization" process has not changed the behavior of the ANDA product following release. Stability data for batches made with Eagle's "optimized" process likewise exhibited upward pH drift from the time of release to the stability test date on the order of 0.05 and 0.06 pH units. DTX-993.0001; DDX7-4. This is sufficient drift to move the pH of Eagle's ANDA product at release from pH 3.59 or 3.60 into the infringing pH range of 3.65-3.94 during the life of the product. Tr. 245:9-246:22, 251:8-14 (Kirsch), 474:7-18 (Park). Accordingly, if Eagle releases a product at the upper end of the release specification, infringement will occur. Tr. 238:6-13, 239:21-246:22, 251:8-14, 251:25-256:8, 317:20-319:6 (Kirsch).

X. EAGLE INFRINGES THE ASSERTED PATENTS

117. Eagle stipulated that its product satisfies every limitation of the asserted claims of the ’785 and ’209 patent, except the limitation from independent claim 1 of each patent that recites “wherein the unit dosage form has a pH of 3.7-3.9.” *See* D.I. 268 (Second Amended Joint (Proposed) Pretrial Order), ¶ 58; June 30, 2021 Hearing Tr. at 65:22-25.

118. Accordingly, Eagle’s ANDA products will be encompassed by each asserted claim if, at any time during their approved shelf-life, they have a pH within the claimed range of 3.7-3.9. *Id*.

119. Based on the trial record, Par has proven by a preponderance of evidence that if Eagle’s ANDA products are manufactured within the upper-end of the proposed release pH specification (i.e., at or above pH 3.60), it is more likely than not that products sold by Eagle will have a pH at or above 3.65 (and less than 3.94), and hence within the infringing range, during their shelf-life. *See* Section IX. Eagle’s refusal to lower the upper limit of its release pH specification is evidence that Eagle can and will use the full scope of its authorization. This was further confirmed by Eagle’s package insert that likewise states that its product is “adjusted … to pH 3.4-3.6,” which is the full range of Eagle’s release specification. PTX-1417 at EAGLEVAS0060906. Dr. Park similarly testified that

Eagle's "optimization batches were made by using new manufacturing changes so that the pH can be more represented between 3.4 and 3.6." Tr. 352:10-16 (Park).

A. Eagle's Infringement of the '785 Patent

120. If its ANDA is approved, Eagle would be authorized to sell such products at any point during their shelf-life, and Eagle would thereby directly infringe the asserted claims of the '785 patent (claims 1, 5 and 8) by selling those products at a point in time when they had a pH within the claimed range. Tr. 251:15-253:4 (Kirsch); *see supra*, ¶¶ 53, 70-86, 96-116.

121. Eagle's principal defense was that having "optimized" its manufacturing process, it would no longer be possible for it manufacture batches with a pH within the upper-end of its release pH specification. *See, e.g.*, Tr. 380:16-22 (Park). The Court should find however, that the evidence demonstrated otherwise.

122. In particular, both experts agreed that future batches of Eagle's product could be expected to have release pH values as high as 0.07 pH units higher than the post-filtration in-process test for a particular batch. Tr. 242:18-245:2 (Kirsch), 461:8-12, 473:13-474:2 (Park); *see supra*, ¶¶ 109-111, 15. As described above in Section VIII.C.2, Eagle's optimization/confirmation batches were made with a narrower in-process pH specification than will be used for commercial batches, and none of Eagle's optimized batches had a post-filtration

in-process pH measurement above 3.50. Accordingly, Eagle's pH data for its optimized batches was not representative of the full scope of what Eagle would be authorized to make if Eagle's ANDA were approved with its in-process specification of 3.42-3.54. *See* Section VIII.C.2.

123. The available stability data for Eagle's "optimized" batches—a significant portion of which the FDA does not have—shows that Eagle has not solved the upward drift problem, as the data shows a tendency for the pH of Eagle's products to drift upward after release, oftentimes within the very first month. *See* Section IX.C. Indeed, all but one of the six batches made using the "optimized" manufacturing process drifted upward in pH after release, by as much as 0.06 pH units. PTX-1442; Tr. 450:17-455:16, 468:19-469:4, 473:13-19, 474:7-12 (Park); *see supra*, ¶ 112-114, 116.

124. Taking these together, these facts demonstrated that if Eagle's ANDA is approved, Eagle would be authorized to release products for commercial sale at a pH that drifts upward over time and into infringing territory during their shelf-life. *See* Section IX.

125. Eagle's product would be labeled to have a 24 month shelf-life when stored in refrigerated conditions (*see, e.g.*, PTX-1417, at EAGLEVAS0060909; PTX-1435, at 30; PTO Ex. 1 ¶ 43), such that Eagle would be permitted to sell its products at times when the pH would be expected to have risen to 3.7 or higher,

and thereby directly infringe the patent. *See* Tr. 251:8-14, 254:17-256:4 (Kirsch); *supra* ¶¶ 96-116.

126. Eagle's other main defense is to point to its stability specification, but the Court should find that specification will not prevent infringement by Eagle.

127. As explained in Section VIII.C.4, the stability specification sets out acceptance criteria that a drug product ***should*** meet throughout its shelf-life. *See* D.I. 276, at 2; Tr. 349:18-20 (Park); 21 C.F.R. §§ 211.166-.167, .170. This is in contrast to the release specifications, which ***must*** be met by each and every commercial batch, and acts as the gatekeeper in determining what products Eagle will or will not be authorized to sell. Section VIII.C.3; Tr. 299:12-23. By contrast, the stability specification comes into play *post hoc* and involves sample testing conducted under much more limited circumstances. *See* Section VIII.C.4; Tr. 299:12-23. In particular, only a small subset of Eagle's commercial product would ever be tested per Eagle's stability protocol and only after infringement could occur. *Id.*; Tr. 220:2-12 (Kirsch).

128. Accordingly, Par has proven by a preponderance of evidence that Eagle would directly infringe the asserted claims of the '785 patent under § 271(a) by selling infringing products. Tr. 251:15-253:4 (Kirsch).

129. Par has also proven by a preponderance of the evidence that Eagle would induce infringing use of its products. Eagle's proposed package insert/label

instructs clinicians to administer its ANDA products to patients in order to increase their blood pressure. Tr. 131:23-132:6, 135:7-138:24 (Coralic). This can occur at any time during the products' shelf-life, including at times when the products have a pH within the claimed range. *See* Tr. 254:17-255:21 (Kirsch); *supra*, ¶¶ 14-15.

130. Clinicians will not test the pH of Eagle's product before they administer it, but will instead administer it at whatever pH it has at the time it is provided for administration to the patient. Tr. 137:18-138:4, 144:16-24, 146:21-147:7 (Coralic). Accordingly, clinicians will infringe the '785 patent, by using an infringing product, whenever the product is provided to them with a pH within the infringing range. *Id*., *see* Tr. 254:17-255:21 (Kirsch). And, Eagle's package insert/label will have encouraged and promoted that infringing use. *Id*.; *see supra*, ¶¶ 14-15. By virtue of this lawsuit and the evidence presented by Par that Eagle's products can and will have a pH of 3.7-3.9 during their shelf-life, along with Eagle's refusal to lower its release pH specification, Par has presented evidence of Eagle's specific intent sufficient to establish by a preponderance of the evidence that Eagle would be liable for inducing infringement of the '785 patent. *See* Section IX.

131. Accordingly, if Eagle's ANDA were approved, Eagle would induce infringement of the '785 patent by instructing medical professionals to administer Eagle's product, after storing the product in refrigeration for up to 24-months, at

times when Eagle's product has a pH between 3.7-3.9. Tr. 254:17-255:21 (Kirsch); *see supra*, ¶¶ 129-130.

B. Eagle's Infringement of the '209 Patent

132. For similar reasons, Par has proven by a preponderance of evidence that if Eagle's ANDA were approved, the commercial sale of Eagle ANDA products would induce infringement of the asserted claims of the '209 patent. S*ee supra*, ¶¶ 120-131.

133. The asserted claims of the '209 patent contain a single method step: "administration" of the claimed vasopressin drug product. Tr. 135:7-138:24 (Coralic). And it is undisputed that Eagle's package insert/label instructs clinicians to practice the claimed method of administration. *See* D.I. 268 (Second Amended Joint (Proposed) Pretrial Order), ¶ 58; June 30, 2021 Hearing Tr. at 65:22-25; Tr. 135:7-138:24 (Coralic).

134. Thus, for the same reasons that Eagle would induce infringing use by clinicians of its ANDA products at times during their shelf-life when they have pH values that fall within the infringing range, so too Eagle would induce clinicians to perform the claimed method of the '209 patent at times when Eagle's ANDA products satisfy the pH limitation. *See supra*, ¶¶ 129-131; Tr. 135:7-138:24 (Coralic), 253:5-254:11, 254:17-255:5 (Kirsch).

135. Eagle's principal defense to induced infringement is that it allegedly lacks the specific intent to induce clinicians to infringe. But, the Court should find that Eagle's specific intent is evident from the circumstantial evidence. *See infra*, ¶ 136.

136. In particular, Eagle's package insert and labeling instructs clinicians to administer Eagle's ANDA product in accordance with the claimed method of administration, which will therefore cause them to infringe any time the clinician administers a vial that has a pH within the claimed range. *See supra*, ¶¶ 129-134. By virtue of this lawsuit and the evidence presented by Par that Eagle's products can and will have a pH of 3.7-3.9 during their shelf-life, along with Eagle's refusal to lower its release pH specification, Par has presented evidence of Eagle's specific intent sufficient to establish by a preponderance of the evidence that Eagle would be liable for inducing infringement of the '209 patent. *See* Section IX.

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Respectfully submitted,

FARNAN LLP

/s/ Michael J. Farnan

Brian E. Farnan (Bar No. 4089)
Michael J. Farnan (Bar No. 5165)
919 North Market St.
12th Floor
Wilmington, DE 19801
Tel: 302-777-0300
Fax: 320-777-0301
bfarnan@farnanlaw.com
mfarnan@farnanlaw.com

OF COUNSEL:

Martin J. Black
Sharon K. Gagliardi
Brian M. Goldberg
Luke M. Reilly
Daniel R. Roberts
DECHERT LLP
Cira Centre
2929 Arch Street
Philadelphia, PA 19104
Tel: (215) 994-4000

martin.black@dechert.com
sharon.gagliardi@dechert.com
brian.goldberg@dechert.com
luke.reilly@dechert.com
daniel.roberts@dechert.com

Attorneys for Plaintiffs Par Pharmaceuti
Inc., Par Sterile Products, LLC, and End
Par Innovation Company, LLC

Robert D. Rhoad
DECHERT LLP
502 Carnegie Center, Suite 104
Princeton, NJ 08540-7814
Tel: (609) 955-3200
robert.rhoad@dechert.com

Jonathan D. J. Loeb, Ph.D
DECHERT LLP
2400 W. El Camino Real, Suite 700
Mountain View, CA 94040-1499
Tel: (650) 813-4995
jonathan.loeb@dechert.com

Blake B. Greene
DECHERT LLP
300 W. 6th Street, Suite 2010
Austin, TX 78701
Tel: (512) 394-3000
blake.greene@dechert.com